Remarks

Title

It is understood that the title is viewed as non-descriptive. However, applicants prefer to defer the issue of what the title should reflect as the claimed invention until that issue has been resolved. At this time, applicants have elected to prosecute a species with the understanding that should these claims be found allowable, the other species will be examined on their merits.

Rejections under 35 U.S.C. §112

Claims 1-6, 8, 11 and 12 were rejected under 35 U.S.C. §112 as non-enabled. This rejection is respectfully traversed.

Animal Models are Predictive of Efficacy

The rejection is initially based on the proposition that the animal models, specifically the rat and rabbit animal models used by applicants, do not correlate well with *in vivo* clinical trial results. Enclosed in response are three papers and abstracts of two others. The abstract of Coats, et al., "Remodelling and restenosis: insights from animal studies" Semin. Interv. Cardiol. 2(3), 153-158 (1997), notes that animal studies in remodeling and its contribution to restenosis have been critical, and correlated with human studies. Farb, et al., "Pathology and Chronic Coronary Stenting in Humans," Circulation, 99:44-52 (1999), paper notes at page 51, col. 2, that "These data in the pig model regarding inflammation and thrombus closely reflect the findings observed in human coronary stenting early after implantation (with a relatively longer duration of healing in humans)." The authors then note that there is a difference in the type of vascular injury in normal arteries of animals as compared to the response in human atherosclerotic arteries. (This may be

one reason why there has been variable correlation with some reported animal models). Komatsu, et al., "Neointimal Tissue Response at Sites of Coronary Stenting in Humans" Circulation 98, 224-233 (1998), reports that animal models are generally predictive (page 230), with dogs being an exception (page 232). Kearney, et al., "Histopathology of In-Stent Restenosis in Patients with Peripheral Artery Disease", Circulation, 95:1998-2002 (1997) correlates results in humans obtained at autopsy with animal studies, beginning at the bottom of page 1999, col. 2. The abstract of Folts, et al., J. Am. Coll. Cardio. 33(2), 295-303 (1999), notes that an animal model, the cyclic flow model of coronary thrombosis, has been useful in predicting which agents are likely to be of benefit in clinical trials.

In summary, the literature supports the use of animal models as predictive of efficacy.

Data demonstrates Efficacy of Inhibiting Integrin-mediated Inhibition

Example 2, beginning on page 22 of the application, shows administration of an antibody to rabbits after arterial injury. The data demonstrated that there was a reduction in neointmal area after deep injury of nearly 40% relative to controls. This data alone indicates that the active agent can be effectively delivered. No adverse effects were noted.

Enclosed with this response if an article by the authors and others which has been submitted to the J. Clin. Invest. entitled "Decreased neointimal formation in Mac-$1^{-/-}$ mice reveals a role for inflammation in vascular repair after angioplasty. This paper describes the role of inflammation in mechanical arterial injury, in particular Mac-1, which when absent results in significantly less intimal proliferation and thickening after injury.

There are numerous protein therapies

The relevance of the comments regarding potential degradation of compound, etc. at pages 3-4 of the office action is not clear. Many pharmaceutical proteins and numerous antibodies are administered to patients as therapeutics, absent side effects, and without loss of function. For example, as shown by the abstract by Topol, et al., "Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication" JAMA 278(6):479-484 (1997).

Rejection under 35 U.S.C. §102(e)

Claims 1-6, 8 and 10 were rejected under 35 U.S.C. §102(e) as disclosed by Simon, et al., Circulation 92(8 Suppl), 1-110 (1995) or U.S. Patent No. 5,770,198 to Coller, et al.. These rejections are respectfully traversed.

The claims are drawn to "an effective amount of a compound specifically inhibiting or reducing leukocyte adhesion or function mediated by an integrin selected from the group consisting of Mac-1, LFA-1, p150,95, and CD11d/CD18" to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue.

As demonstrated by Deitch, et al., "Effects of beta3-integrin blockade (c7E3) on the response to angioplasty and intra-arterial stenting in atherosclerotic non-human primates" Arterioscler. Thromb.Vasc. Biol. 18(11):11730-1737 (1998), the results obtained with c7E3 "were not from inhibition of intimal hyperplasia or improved artery wall remodeling.".

This evidence demonstrates that this antibody ("Reopro") does not affect restenosis. Therefore neither Simon, et al., nor Coller, et al. disclose the claimed subject matter.

Rejections under 35 U.S.C. §103

Claims 1-6, 8, and 10-12 are rejected under 35 U.S.C. §103 are non-obvious over Ricevuit, et al., Atherosclerosis 91, 1-14 (1991) and/or Albelda, et al., FASEB J. 8:504-512 (1994), and/or U.S. Patent No. 5,770,198 to Coller,et al. or Simon, et al., Circulation (1995), in view of unidentified art for administering pharmaceutical compositions and Neumann, et al., JACC 27, 819-824 (1996). These rejections are respectfully traversed.

Simon and Coller

Simon and Coller are discussed above.

Ricevuti

Ricevuti, et al., discusses the role of granulocytes in endothelial injury, as examined by reacting a monoclonal antibody to CD11b/CD18. As the examiner correctly notes, this paper relates to **ischemia and reperfusion; not restenosis.**

Albelda, et al.

Albelda, also discusses the role of antibodies to CD11/CD18 integrins to endothelial ligands such as intercellular adhesion molecule-1 (ICAM-1) involved in inflammation and, as the examiner has noted, "to inhibit neutrophil influx in almost every system to date including the heart and ischemia reperfusion". However, there is no mention of preventing restenosis.

Neumann, et al.

Neumann measured the presence of several molecules on platelets, before and after dilated coronary artery plaque. The results demonstrated that there was increased expression of the activated fibrinogen receptor LIBS1 on platelets as well as Mac-1 (CD11b) and L-selectin

(CD62L) on neutrophils, indicating genrally that there was neutrophil and platelet activation at the injured artery.

Summary

The art cited by the examiner relates to reperfusion and ischemia (Albelda and Ricevuti), not restenosis; platelet and neutrophil activation generally following arterial activation (Neumann); and an antibody which may be cross-reactive with Mac-1 *in vitro* but is not cross-reactive *in vivo,* nor does it demonstrate any clinical effectiveness against restenosis.

Results obtained relative to ischemia and reperfusion are not predictive of results obtained in the treatment of restenosis. The mechanisms are different, the treatments are different, the outcomes are different. Even the markers associated with restenosis are different from those associated with reperfusion. No art has been cited which would indicate that there is any teaching that ischemia is predictive of restenosis. Therefore, compounds which relate to the treatment of ischemia and reperfusion are not encompassed by the claims. No compounds which "specificaly inhibit or reduce leukocyte integrin-mediated adhesion or function", as required by claim 1, have been associated with treatment or prevention of restenosis, as required by the claims, much less is there any teaching in the cited art that would lead one skilled in the art to use compounds known for the treatment of ischemia for the treatment of restenosis, even less so with any expectation of success. Therefore the claimed subject matter cannot be obvious from the cited art.

Response to Notice to Comply with Sequence Rules

Responsive to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence disclosures mailed on 23

November 1998, in the above-identified application, Applicants enclose a 3 & 1/2" diskette containing a computer-readable form of the Sequence Listing as well as a paper copy of the Sequence Listing. Applicants also enclose a copy of the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures.

Declaration under 37 C.F.R. § 1.821(f)

I declare that the material on the diskette is identical to the enclosed paper copy of the Sequence Listing and the sequences as filed in the application on 25 March 1997, that the Sequence Listing does not add new matter to the application, and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Allowance of all pending claims 1-12 is earnestly solicted in view of the foregoing remarks and accompanying materials.

Respectfully submitted,

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U.S.S.N.: 08/823,999
Filed: March 25, 1997
AMENDMENT

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this , along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: May 24, 1999

Patrea L. Pabst